

Remarks

Claims 1, 7-11, 14, 15, 17-21, 24, 34, 43, 56, and 78-86 were previously pending and under examination. By this Amendment claims 1, 7, 10, 11, 20, 21, 24, 34, 43, 56, and 86 are currently amended, no claims are canceled, and new claims 87-104 are presented. No new matter is introduced. As a result, claims 1, 7-11, 14, 15, 17-21, 24, 34, 43, 56, and 78-104 are currently pending and under examination.

Claim 1 is currently amended to specify that cells of the B-cell malignancy upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide and that the antibody is specific for the upregulated antigen. The limitation that the antigen is CD20 has been dropped from claim 1 and is now incorporated into claim 7, which depends from claim 1. Claims 10, 11, 20, and 21 are currently amended so as to depend from claim 7 rather than from claim 1. New claim 93 depends from claim 1 and adds the limitation that the immunostimulatory CpG oligonucleotide is ODN 2006 (SEQ ID NO:729). Support for this limitation can be found throughout the specification, including for example at page 9, line 74.

Claim 24 is currently amended to specify that cells of the marginal zone lymphoma or B-cell chronic lymphocytic leukemia upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide and that the antibody is specific for the upregulated antigen. The limitation that the antigen is chosen from CD19 or CD22 has been dropped from claim 24 and is now incorporated into new claims 94 and 95, which depend from claim 24. New claims 96-98, which also depend from claim 24, have parallel construction to claims 14, 17, and 19, respectively. New claim 99 depends from claim 24 and adds the limitation that the immunostimulatory CpG oligonucleotide is ODN 2006 (SEQ ID NO:729).

Claim 34 is currently amended to specify that the cells of the B-cell malignancy upregulate expression of a surface antigen in response to immunostimulatory CpG oligonucleotide and that the antibody is specific for the upregulated surface antigen. The limitation that the B-cell malignancy is a marginal zone lymphoma or B-cell chronic

lymphocytic leukemia has been dropped from claim 34; this limitation is set forth in previously presented claims 81 and 82, which depend from claim 34. The limitation that the surface antigen is selected from CD19, CD20, and CD22 has been dropped from claim 34; this limitation is now set forth in previously presented claims 78-80, which depend from claim 34. The limitation that the antigen is not expressed or is expressed in an amount lower than that of a normal B cell is currently amended to the latter alone, i.e., claim 34 now specifies only that the antigen is expressed in an amount lower than that of normal B cells. The former limitation, i.e., that the antigen is not expressed, is now found in new claim 100, which depends from claim 34. New claims 101-103, which also depend from claim 34, have parallel construction to claims 14, 17, and 19, respectively. New claim 104 depends from claim 34 and adds the limitation that the immunostimulatory CpG oligonucleotide is ODN 2006 (SEQ ID NO:729).

Claim 43 is currently amended to specify that cells of the B-cell malignancy that is resistant to therapy with an antibody specific for a surface antigen upregulate expression of the cell surface antigen in response to immunostimulatory CpG oligonucleotide. Claim 43 is further amended to specify that the subject is administered an antibody specific for the upregulated surface antigen. The limitation that the surface antigen is chosen from CD19, CD20, and CD22 has been dropped from claim 43; this limitation is now set forth in previously presented claims 83 and 84 and in claim 86 as currently amended, which depend from claim 43. Claim 86 is currently amended to refer to CD22 rather than CD20, which was already specified by claim 84. The limitation that the B-cell malignancy is a marginal zone lymphoma or a B-cell chronic lymphocytic leukemia has been dropped from claim 43; this limitation is now set forth in new claims 87 and 88, which depend from claim 43. New claims 89-91, which also depend from claim 43, have parallel construction to claims 14, 17, and 19, respectively. New claim 92 depends from claim 43 and adds the limitation that the immunostimulatory CpG oligonucleotide is ODN 2006 (SEQ ID NO:729).

Claim 56 is currently amended to specify the cells of the cancer upregulate expression of a surface antigen in response to immunostimulatory CpG oligonucleotide and the

immunostimulatory CpG oligonucleotide is administered in an effective amount to upregulate expression of the surface antigen by the cancer.

Prior Office Action

Applicant thanks the Examiner for indicating that the information disclosure statements (IDS's) submitted to the Patent Office October 1, 2001, September 30, 2002, and January 28, 2004, have been considered.

Previous Claim Rejections Under 35 U.S.C. § 112, first paragraph

Applicant acknowledges the Examiner has withdrawn all previous claim rejections under 35 U.S.C. § 112, first paragraph.

Maintained Claim Rejections Under 35 U.S.C. § 103

Beginning at page 3 of the Office Action, the Examiner indicated that claims 1, 7, 8, 9, 10, 11, 14, 15, and 17-21 stand rejected under 35 U.S.C. § 103(a) over Wooldridge et al. (*Blood* 89:2994-2998 (1997)) in view of various additional references (Taji et al., *Japanese Journal of Cancer Research* 89:748-756 (1998); Winkler et al., *Blood* 94:2217-2224 (1999); Pawade et al., *Histopathology* 27:129-137 (1995); and/or Ramasamy et al., U.S. Pat. 5,969,135) previously made of record. For reasons provided below, Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw the rejection of claims 1, 7, 8, 9, 10, 11, 14, 15, and 17-21 under 35 U.S.C. § 103.

As noted above, Applicant has amended claim 1 to add the limitation that cells of the B-cell malignancy upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide and the antibody is specific for the upregulated antigen.

Applicant has made the unexpected discovered that administration of an immunostimulatory CpG oligonucleotide induces the expression of certain cell surface antigens, including CD19, CD20 and CD22, and that the induction of these antigens lends itself to enhanced antibody-dependent cellular cytotoxicity (ADCC) directed toward malignant cells expressing these particular antigens (see page 11, first paragraph of the specification). Further,

Applicant has made the surprising discovery that an inverse correlation exists between baseline expression of specific cell surface antigens and their expression after exposure to an immunostimulatory CpG oligonucleotide, the most significant increase in expression occurring in cells that had the lowest or no baseline levels (see page 12, first paragraph of specification). In other words, Applicant has made the unexpected discovery that administration of an immunostimulatory CpG nucleic acid to malignant B cells lacking or having only low level expression of certain antigens upregulates expression of the antigen(s), resulting in an unexpectedly efficient antibody response.

Claim 1 as currently amended adds a limitation that goes to selection of the B-cell malignancy to be treated based on the unexpected and previously undisclosed property of cells of that malignancy to upregulate expression of certain antigens in response to immunostimulatory CpG oligonucleotide. This same limitation similarly goes to selection of the antibody based on the unexpected and previously undisclosed property of target cells of the malignancy, in response to immunostimulatory CpG oligonucleotide, to upregulate expression of antigen recognized by the antibody.

Neither Wooldridge et al. nor any other reference cited by the Examiner teaches or suggests that administering an immunostimulatory CpG oligonucleotide to malignant B cells upregulates expression of the claimed antigen(s), thereby guiding selection of an antibody specific for an upregulated antigen, as claimed. Significantly, neither do any of the references, when taken in combination as suggested by the Examiner, teach or suggest this selection limitation. A skilled person would not have found motivation to select a B-cell malignancy, the cells of which upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide, for treatment with CpG and an antibody specific for the antigen that is upregulated in response to immunostimulatory CpG oligonucleotide because such malignancies and such antigens were previously unknown. Applicant therefore respectfully submits that claim 1 as currently amended would not be obvious over Wooldridge et al. in view of any of the various additional references previously made of record. Accordingly, Applicant respectfully

requests the Examiner to reconsider and withdraw the maintained rejection of claims 1, 7, 8, 9, 10, 11, 14, 15, and 17-21 under 35 U.S.C. § 103(a).

New Claim Rejections Under 35 U.S.C. § 103

Beginning on page 4 of the Final Office Action the Examiner indicated that claims 24, 34, 43, and 78-86 are rejected under 35 U.S.C. § 103(a) as obvious over Wooldridge et al. (*supra*) in view of Goldenberg (U.S. Pat. 6,306,393), and in some instances further in view of specific additional references (Winkler et al., *supra*; Pawade et al., *supra*). For reasons provided below, Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw the rejection of claims 24, 34, 43, and 78-86 under 35 U.S.C. § 103(a).

As noted above, Applicant has amended claims 24, 34, and 43 to add the limitation that cells of the B-cell malignancy upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide and the antibody is specific for the upregulated antigen.

Also as noted above, Applicant has discovered that the administration of an immunostimulatory CpG oligonucleotide induces the expression of certain cell surface antigens, including CD20, CD19 and CD22, and that the induction of these antigens lends itself to enhanced ADCC directed toward malignant cells expressing these particular antigens (see page 11, first paragraph of the specification). Further, Applicant has made the unexpected discovery that an inverse correlation exists between baseline expression of specific cell surface antigens and their expression after exposure to an immunostimulatory CpG oligonucleotide, the most significant increase in expression observed in cells having the lowest or no baseline levels (see page 12, first paragraph of specification).

Each of claims 24, 34, and 43 as currently amended includes a limitation that goes to selection of the B-cell malignancy to be treated based on the unexpected and previously undisclosed property of cells of that malignancy to upregulate expression of certain antigens in response to immunostimulatory CpG oligonucleotide. This same limitation similarly goes to selection of the antibody based on the unexpected and previously undisclosed property of target

cells of the malignancy, in response to immunostimulatory CpG oligonucleotide, to upregulate expression of antigen recognized by the antibody.

There is no teaching, suggestion, or motivation provided by Wooldridge et al., Goldenberg, or the combination of Wooldridge et al. and Goldenberg to select a particular B-cell malignancy for treatment with CpG and antibody on the basis of the property of cells of the malignancy to upregulate expression of antigen recognized by the antibody in response to immunostimulatory CpG oligonucleotide. Therefore Applicant's invention is not obvious over Wooldridge in view of Goldenberg. The various additional references do not remedy this deficiency with respect to the combined teachings of Wooldridge et al. and Goldenberg. Thus it is respectfully submitted that claims 24, 34, 43, and 78-86 are not obvious over Wooldridge et al. and Goldenberg, even when taken in view of these other cited references. Applicant therefore respectfully requests the Examiner to reconsider and withdraw the rejection of claims 24, 34, 43, and 78-86 under 35 U.S.C. § 103(a).

The examiner rejected claim 56 under 35 U.S.C. § 103(a) as unpatentable over Wooldridge et al. in view of Micouin et al., *Leukemia* 1:552-560 (1997). Micouin et al. teaches the use of antigen-nonspecific human IgG1 capable of inducing differentiation of leukemia HL-60 and U937 cells (see page 554, column 2, last paragraph). In contrast, claim 56 is directed to the use of an antigen-specific human IgG1 antibody that recognizes a surface antigen on a cancer cell to be treated, in combination with CpG. There is no teaching, suggestion, or motivation to make the proposed combination of Wooldridge and Micouin because Wooldridge teaches use of an antigen-specific antibody and Micouin teaches use of antigen-nonspecific antibody. Even if one were to combine the references as suggested by the examiner, it is evident that there is no way properly to combine the teaching of Wooldridge with the teaching of Micouin to arrive at the claimed invention. Therefore claim 56 is not obvious over Wooldridge in view of Micouin. Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claim 56 under 35 U.S.C. § 103(a).

Summary

Claims 1, 7, 10, 11, 20, 21, 24, 34, 43, 56, and 86 are currently amended, no claims are canceled, and new claims 87-104 are presented.. Applicant believes that the claims are in condition for allowance. An early and favorable response is earnestly solicited. The Examiner is invited to contact the undersigned by telephone to discuss any remaining issues of patentability.

Respectfully submitted,

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